Medical Progress

The Nature and Treatment Of Stress Ulcers

A Review

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STRESS ULCERATION of the gastrointestinal tract was recorded by the ancients. Twenty centuries ago Celus observed this phenomenon in men suffering the extraordinary tensions of a rigorous military campaign. No doubt it has been with us from the very start of man's indulgence in warfare. As we have shown no particular inclination to give up this aspect of human activity, one may predict stress ulcers will remain with us for the foreseeable future. While war may represent the ultimate in stress, the life of the civilian is hardly without great tension. The extreme physiologic agitation which may lead to ulceration in a combat soldier finds its parallel in the stresses and strains of a major operation or in local or systemic disease processes of unusual virulence and magnitude.

Definitions and Nomenclature

In medicine, as in virtually all science, definition often takes the form of classification. Medical classification is based upon clinical behavior, on morphologic appearance or on known or implied etiologic factors. Those who do the classifying use one or the other of two fundamentally very different approaches. There are the lumpers and the splitters. The lumpers tend to put many or all examples of a certain problem into the same category and sometimes a single word or apt phrase may be found or coined to identify and accurately represent the whole problem. The splitters earn that epithet: As soon as a species (in natural history, for example) is defined, they gleefully go about discovering and describing more or less numerous subspecies. (One need but think for a moment of the species man—Homo sapiens—to recognize in himself the natural tendency toward lumping or splitting.) It is difficult to say which approach, when diligently pursued and translated into therapeutic action, comes closest to the truth. Stress ulcer is a wonderful example of this very thorny problem. If it could be simply defined, perhaps it could be simply or at least uniformly treated with a higher degree of success. Unfortunately, this little corner of utopia is not yet well mapped. Even in attempts to define the word *stress,* the problem becomes almost impossibly complex. There are knowns as well as unknowns, however, and it is upon these that attention should be focused.

Pathologic Anatomy

If one word could be used to describe the appearance of a stress ulcer under the microscope, that word would be *acute.* Figure 1 illustrates a typical example. The ulcer penetrates deeply but there is little or no evidence of fibrosis (chronicity). Much fibrin and numbers of acute inflam-

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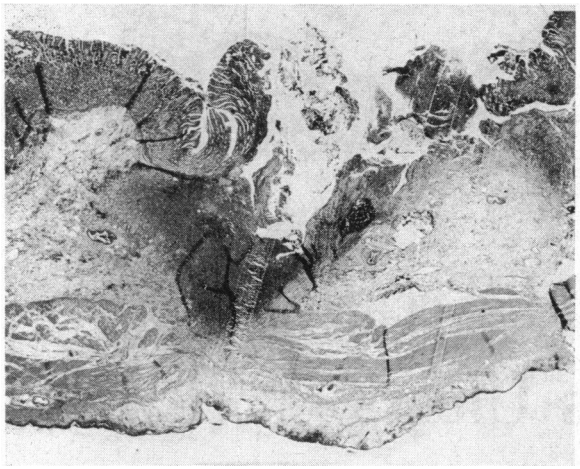

Figure 1.— Photomicrograph showing a typical stress ulcer (×10). There is evidence of acute inflammation but no fibrosis.

matory cells frequently are present. The borders between the ulcerated region and the adjacent mucosa are often surprisingly sharp, but other areas of the involved organ may show changes which possibly represent the beginnings of a second ulcer or erosion (Figure 2). Very pronounced vascular congestion is the striking feature of the latter lesions. It is not difficult to imagine that dissolution of the surface mucosa is the next step (Figure 2).

The anatomic location of such ulcers is of great clinical importance. The widely held impression that stress ulcers are always numerous and have a tendency to involve the entire organ is not sustained by the facts.[1,2] Table 1 is a summary view of our own autopsy material over the past five years. When multiple ulcers were present, they tended to appear as satellites grouped about a larger and apparently primary lesion. Hence, although two to five or more ulcers were present in a number of cases, large portions of the involved organ still were spared. When multiple gastric ulcers did occur, they were located in the antrum or antrum and lower body in two-thirds of our cases. When combined with duodenal lesions, the ulcers were always antral in location.

TABLE 1.—*Relative Incidence of Single and Multiple Stress Ulcers as Noted in Autopsy Material in a Five-Year Period*

Single gastric	8
Single duodenal	9
Multiple gastric	25
Multiple duodenal	7
Combined gastric and duodenal	9

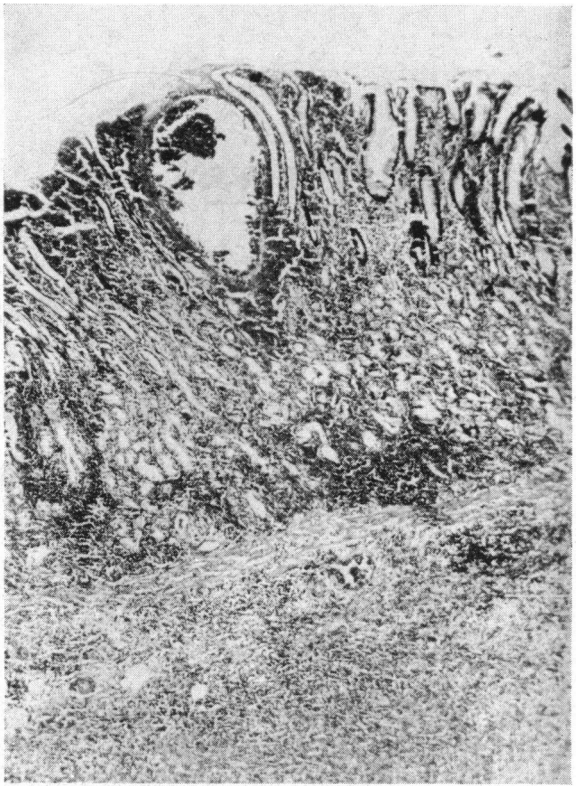

Figure 2.—Photomicrograph illustrating massive vascular congestion at the mucosal surface, perhaps the early stage of an oncoming frank ulceration (×100).

Curling's original report[3] described only duodenal lesions occurring in association with burns. Several of Cushing's patients also died of duodenal rather than gastric lesions.[4]

Reports in the literature[5,6] show about 30 percent of stress ulcers are duodenal, with gastric or combined gastro-duodenal ulcers accounting for most of the remainder.

Acute ulcers of the esophagus, jejunum, and colon also have been described.[4,7,8] The small and large bowel lesions appear to be agonal, but the reports of esophageal lesions are more difficult to interpret.[4,8] A beautiful drawing of a huge perforated esophageal ulcer appears in Cushing's classic article.[4] Cushing considered esophageal involvement as part of the same overall process. In our own necropsy series, 7 of 58 patients had esophageal ulcers or erosions, some of which had perforated, death quickly following. In each of the patients with esophageal ulcers violent and prolonged retching and vomiting, whatever the cause, dominated the clinical manifestations. The implication that these lesions were the result of such vomiting or retching or both is clear.

TABLE 2.—*Diseases Associated with Acute Peptic Ulcer (51 Autopsy Cases—UC Irvine Series)*

Cases		Ulcer: Primary Cause of Death	Ulcer: Contributing Cause of Death	Ulcer: Agonal only
12	Central nervous system	6	4	2
12	Malignant tumors	7	2	3
7	Infections	4	2	1
9	Cardio-respiratory disease	4	4	1
4	Renal failure	1	1	2
6	Liver disease	5	0	1
1	Amyloidosis	0	1	0

Etiology

The exact cause of stress ulceration, at least as expressed in precise and unequivocal terms, is unknown. A strong case for guilt by association can be made, however. The associations are varied almost without limit. The stress, whatever it may be, is always extraordinarily severe. If it be a thermal burn, the burn is extensive or complicated.[6,9,10,11] If it be operation, the procedure is usually long and accompanied by complications during or soon after operation, or is performed on an organ more vital than most, such as the heart.[12] Sometimes the "simpler" procedures or diseases are also severely stressful enough to be causative associates; there are many reported examples[8,13] in association with appendicitis and appendectomy, strangulated hernia and herniorrhaphy.

The classic association with central nervous system tumor or trauma is well known. The reader's empathy and sympathy pours out to Cushing as he describes his helpless feeling of frustration and despair in relating the tragic ending of an otherwise successful removal of a brain tumor in death by exsanguination or perforation of a stress ulcer.[4] Birth trauma[8] and bulbar poliomyelitis[14] are other examples of central nervous system lesions which may be associated with acute ulceration. Bulger[15] reported upon a youngster (18 months old) who died following a snake bite. The snake was not identified, but as the venom is frequently specifically neurotoxic, it is of interest to note that coma and violent convulsions preceded the appearance of ulceration.

Even mental disease may precipitate a stress ulcer.[16] There are other examples, such as myocardial infarction,[17] too numerous to list. Some of them are shown in Table 2.

Many of the numerous and varied reported cases do have some things in common. The most striking is sepsis or shock. This association has been

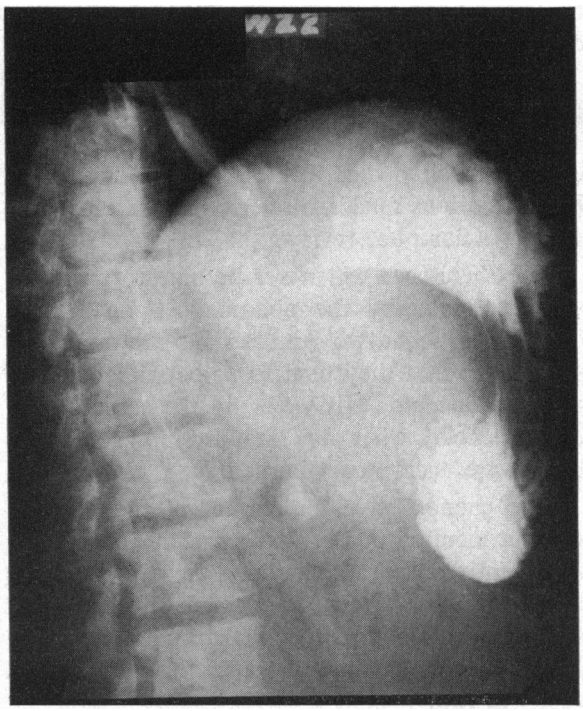

Figure 3.—X-ray film showing huge pancreatic pseudocyst in a 29-year-old man in whom stress ulcer subsequently developed. (Case described in text.)

noted and dwelt upon by several investigators.[7,8,13] Billroth[13] considered septic emboli to the gastric mucosa to be primarily responsible for death due to stress ulcer in a case in which he partially removed a huge substernal goitre.

The observation that many examples of stress ulcers, when studied microscopically, show widespread vascular thrombosis or congestion or both, has led to the view that hypoxia or hypotension may be specifically responsible for their development.[18,19] Experimental studies lend considerable support to this impression.[20] Harjola and Sivula[21] recorded some fascinating observations in rabbits. An initial episode of bleeding revealed a pale, white, relatively bloodless gastric mucosa. With restoration of blood volume several dark (hemorrhagic) spots would appear for a moment, then be gone. Repeated bleeding to the point of shock, however, led to frank dissolution and ulceration of parts of the gastric mucosa in many animals. The ulcers appeared in the very areas that became congested during the first bleed.

A different tack in experimental work was taken by French and Porter,[22] who found that acute gastrointestinal ulceration followed electrical stimulation of the hypothalamus in cats and that the effect

could be blocked in some instances by interruption of the vagus pathways.

Harkins[1,2] tabulated no fewer than 28 theories proposed as to how and why stress ulcers develop. The basic or most plausible of them have been covered or alluded to in the foregoing discussion, but the curious reader is referred to Harkins' articles for a complete review.

One theory we will never be able to pursue is that expressed by the ubiquitous John Hunter whose ideas from two centuries ago are frequently so modern that they tend to agree with our own current concepts. His views on the subject went up in smoke when the manuscripts containing them were accidentally burned.[4]

One cannot leave this aspect of the problem without mention of Dr. Wangensteen's angry dog. Apparently an enraged bulldog died from the effects of multiple stress ulcers which appeared after a spirited fight with one of his laboratory mates.[23] It is of interest to note that at autopsy the gastric acid was low.

Clinical Behavior

The one clinical characteristic that all stress ulcers seem to have in common is that they appear without obvious warning and with dramatic suddenness. Prodromal symptoms and signs are absent. The only suggestion of an impending storm or disaster may be abdominal distension or ileus, though this is by no means always present. Hemorrhage of massive proportions or the effects of perforation simply present as both a fact and a challenge. The timing varies from a few hours after injury or operation to several weeks later. The great majority occur around the fifth to seventh day, or certainly within the first two weeks.[24] It is of great interest to note that if an acute stress ulcer is survived, with or without operation, there is little or no tendency to recurrence.[25]

Diagnosis and Treatment

Observation in the necropsy room or operating theater is the only certain method of establishing the diagnosis. So many of the patients are so ill and kept to their beds by the primary disease process or by the encumbrance of a multitude of traction devices, cardiographs and intravenous tubing, that gastroscopy or radiography is seldom used. Both may be helpful, as they are in any diagnostic problem involving upper gastrointestinal hemorrhage. The diagnosis can certainly be very strongly suspected by association with a particularly stressful setting.

The difficulty of the therapeutic challenge is obvious to most of us from personal experience. The outlook has been indeed grim. Table 2 indicates how overwhelming the seriousness of the associated or precipitating disease processes may be. The table also indicates, however, that more often than not it was the ulcer that brought death. A characteristic of such cases is that often in retrospect there is the haunting thought that perhaps some of these unfortunate patients might have been saved with a well conceived and timely operation.

While it is true that some patients are basically untreatable, others are simply untreated (save for blood transfusion). The results tend to be poor.[7,25] Yet some patients do stop bleeding and recover with transfusion and other more obscure forms of non-surgical methods. Where does one draw the line? We "waited out" one of our patients to the total of 22 units of blood administered during the first postoperative week. This patient weighed over 400 pounds and had had jejunoileal bypass for exogenous obesity. Perhaps the surgeon's spirit was broken by the prospect of reoperation for control of hemorrhage in this case. In any event, bleeding stopped and the patient survived.

In another of our cases, dye was injected into the pancreas by misdirection in an attempt at aortography (at another hospital). Necrotizing pancreatitis was followed by shock, septicemia and pancreatic pseudocyst formation (Figure 3). The temperature reached 42.2°C (108°F). Somehow the patient survived all this; then bleeding began from a stress ulcer. The ulcer was suture ligated, the reasoning being that the patient's condition was such that he could not stand anything else. Bleeding recurred, and at reoperation the single gastric ulcer was found to have enlarged and to be bleeding furiously. It was excised and vagotomy and pyloroplasty were performed. The patient survived. These two cases emphasize that the most critical judgment must be exercised in deciding for or against operation in any individual case—operation according to the general rules, is the way Dalgaard[26] expresses it; or, in the words of Fogelman and Garvey,[25] "critically ill patients can withstand surgery better than they can withstand continuing hemorrhage, recurrent shock, and progressive deterioration."

Therapy: Choices, Results, and Rationale

It is not possible to make valid comparison of results as between non-surgical and surgical therapy. One reason is that in many patients non-operative treatment is not "elective" but is decided upon simply because of the incurable or hopeless nature of the primary disease. In other cases the bleeding ceases, does not recur, and the question of operation is never brought up. For that mattter, the diagnosis is never really confirmed.

In the case of massive bleeders—patients who require five or more units of blood to maintain a reasonable volume during the crisis—the results of non-operative therapy are very bad. The reported mortality rates vary from 60 to 100 percent.[7,25,27]

Until the 1940s few patients had been operated upon for stress ulceration.[1,2] As recently as 1951, no survivals had been reported.[25] Since that time, reports of an increasing number of successes with operation have appeared in the surgical literature.[7,23,24,25,27,28,29,30]

Operations of various types have been used. At first it was local treatment with excision, closure or suture of the ulcer or ulcers, but often control of hemorrhage was not achieved and the ulcerative process progressed. More radical measures were tried. For a time a gastric resection, often quite high, was used. Although at times the procedure was successful, many deaths occurred. The logical next step in the search for improvement was vagotomy and pyloroplasty combined with local treatment of the ulcer. This is an "in between" procedure somewhat more simple to perform than resection and considerably more effective than local treatment alone. Current experience definitely seems to favor it (Table 3).

At first it was feared, not unreasonably, that *any* operation would end in disaster. After all, how could one operate through a burn wound and expect the suture lines to heal? Sometimes they did not. Hummel[10,11] reported two deaths after resection in such circumstances. One recalls Billroth's fear of elective operation on the stomach, wondering whether the gastric acid would dissolve away the closure of a gastrotomy incision.[31] The suture line healed in his first patient, and so they have in many cases since even when the patients were burned or otherwise badly injured.

At first glance the logic of a resection, with excision of the stressed mucosa and the mechanism that produced the ulceration, is difficult to argue against.

Two major objections can be raised, however. One is that stress ulcers do not often recur. The other is the prospect of problems and sequelae that are entailed in loss of much or most of the stomach forever. If the more conservative operation of vagotomy and pyloroplasty (plus local treatment) is really effective, and it seems to be, it obviously is the better procedure to use.

There is some scientific basis for the belief that vagotomy plays a key role in the control of stress bleeding. Womack and Peters[32] documented the fact that vagus section will result in the opening of submucosal and mucosal arteriovenous shunts in the gastric wall, with the result that blood is diverted from the surface mucosa to a significant degree, bleeding is thereby arrested and healing can go forward.

The effect of vagotomy on acid secretion during stress ulceration is less clear. There is no agreement that hyperacidity, relative or absolute, occurs

TABLE 3.—*Results of Surgical Operation for Peptic Ulcer*

	Resection		*Re-Bleeding*		*Local Treatment*		*Re-Bleeding*		*V & P*		*Re-Bleeding*		*By-Pass*	
Reported by	*Survivors*	*Deaths*	*Survivors*	*Deaths*	*Survivors*	*Deaths*	*Survivors*	*Deaths*	*Survivors*	*Deaths*	*Survivors*	*Deaths*	*Survivors*	*Deaths*
Hummel	0	2	..	..	..	..	..	..	..	..	..	..	..	..
Goodman and Frey	0	2	0	1	0	2	0	2	6	3	2	3	..	..
Wright	0	1	0	1	0	1	..	..	..	..	..	..	..	..
Fogelman and Garvey	4	1	..	..	..	..	..	..	1	2	..	..	0	1
Moncrief	1	5	0	1	..	..	..	..	0	1	0	1	..	..
Griffin	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Biel	6	9	..	..	1	3	..	..	..	..	..	..	..	..
Gilchrist	3	0	..	..	..	..	..	..	..	..	..	..	..	..
Braithwaite	1	0	..	..	..	..	..	..	..	..	..	..	..	..
Wangensteen	2	3	..	..	..	..	..	..	..	..	..	..	..	..
Salasin	1	0	..	..	..	..	..	..	..	..	..	..	..	..
Bryant and Griffin	..	..	..	..	..	..	..	..	5	0	2	3	..	..
Kirtley, et al.	3	4	0	1	4	4	1	1	18	8	1	3	..	..
Nagel	0	4	..	..	1	1	..	..	6	2	0	1	..	..

at all. Dragstedt[33] thinks not. Yet the old adage "no acid, no ulcer" probably holds as well for stress ulcer as it does for the more typical variety.

Bryant and Griffin,[34] almost alone among recent observers, expressed belief that vagotomy and pyloroplasty is not the procedure of choice. All five of their patients had recurrence of bleeding and three died as a result. Their experience serves to emphasize there is no panacea and no perfect operation for this problem. Rebleeding does occur (as it does with gastrectomy also) and this complication ends in death far more often than not. Cumulative experience (Table 3) indicates, however, that the prospects for a successful outcome are significantly higher with vagus section and drainage than with either local treatment or subtotal gastrectomy.

In conclusion, it should be stated that the mortality rates in operation for stress ulcer tend to increase in direct proportion to delay in operation, no matter what procedure is used. The need for a carefully considered, but nonetheless quick decision is as great in dealing with this problem as it is in the management of a patient who is bleeding from a more typical peptic ulcer.

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EXAMINING FOR UNDESCENDED TESTES

"The best position for examining a boy for undescended testes is to have him sit in a chair or on the examining table with his back against the wall and his heels brought up against his buttocks. The other technique . . . which is particularly helpful in the younger child, before cooperation is possible, is to apply some soap to the fingers and to rub the soapy fingers over the inguinal area. You will pick up the sensation of a testis rolling underneath your fingers when sometimes you cannot feel it."

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